

PATENT SPECIFICATION

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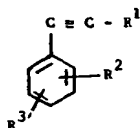


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(54) SUBSTITUTED ACETYLENIC COMPOUNDS

(71) We, CHINOIN GYOGYSZER ES VEGYESZETI TERMEKEK GYARA RT., a body corporate organised under the laws of Hungary, of 1-5 To u., Budapest IV, Hungary, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to new substituted phenyl-acetylenes and a process for the preparation thereof. The new phenylacetylenes have the general formula I



wherein

(a) R¹ is alkyl of 5 or 6 carbon atoms or diaralkyl wherein the alkyl moiety has 2—6 carbon atoms;

R² is hydrogen or halogen; and

R³ is hydrogen, alkyl having 1 to 6 carbon atoms, aralkyl having 1 to 6 atoms in the alkyl moiety, aryl or aryloxy or an aroyl group of the general formula ArCO, wherein Ar is phenyl or a 2-thienyl group;

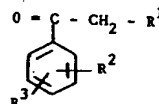
with the proviso that R² and R³ are not both hydrogen; or (b) R¹ is hydrogen, alkyl having 1 to 6 carbon atoms, aralkyl wherein the alkyl moiety has 1 to 6 carbon atoms, or diaralkyl wherein the alkyl moiety has 2 to 6 carbon atoms,

R² is halogen; and

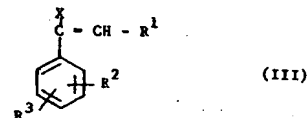
R³ is hydrogen; with the proviso that when R¹ is methyl and R³ is hydrogen, R² is not m-chloro, p-chloro, p-bromo or p-fluoro.

The new compounds of the formula I can

be prepared by reacting a compound of the general formula II



wherein the substituents are as defined above, with a halogenating agent, preferably with a phosphorus halide, and reacting the compounds thus obtained of the general formula III



wherein the substituents are as defined above, if desired without isolation, with a strong base.

According to an advantageous embodiment of the present invention, compounds of the general formula II are reacted with phosphorus pentachloride without any solvent or in an organic inert solvent, such as diethylether at a temperature of 20 to 100°C, preferably at the boiling point of the solvent. The reaction may be carried out in the solvent, preferably, at a temperature of 50 to 90°C.

The hydrogen halide can be split off with strong bases, preferably with alkali metal hydroxides, such as potassium hydroxide or alkali metal alcoholates, such as sodium methoxide or sodium or potassium tert. butoxide, preferably in an organic solvent. As an organic solvent alcohols, or aromatic hydrocarbons, preferably toluene, may be used.

Hydrogen halides are preferably split off

with sodium methoxide and as a solvent preferably dimethylsulfoxide or dimethylformamide are used.

The hydrogen halide is split off preferably at 20 to 130°C, advantageously at the boiling point of the solvent employed; the preferred solvent dimethylsulfoxide boils at 70°C.

On a large-scale the hydrogen halide may be split off by subjecting the halo-olefin of general formula III to dehydrohalogenation without purification or isolation.

The phenyl-acetylene compounds of the general formula (I) can be used in the pharmaceutical industry, primarily as intermediates for the preparation of valuable pharmaceutically active phenylalkyl carboxylic acids (cf. our copending Application Serial No. 1,552,202). Hitherto the compounds of the present invention had not been prepared because of technical problems with the known synthetic routes, such as the unavailability of the starting materials. The synthesis of compounds related to those of general formula (I) by the above-described route is further illustrated in our Hungarian Patent Application No. CI-1668 laid open under number T/15127 (equivalent to our Spanish Patent No. 459,087).

One embodiment of our invention is illustrated in the following Example.

Example

41.6g. of *m*-bromo-propiophenone and 52g. of phosphorus pentachloride are heated on a water bath at 75°C until evolution of hydrogen chloride ceases, i.e. for about 20 to 25 minutes. After cooling, the reaction mixture is fractionated *in vacuo*. The cut of boiling point 108—112°C at 1.5 mmHg (31g.) is dissolved in 150 ml. of anhydrous toluene, 70g. sodium tert. butoxide are added and the mixture is heated for 7 hours under vigorous stirring. The reaction mixture is decomposed with water, the two layers are separated and the aqueous layer is extracted with 3×100 ml. of toluene. The toluene is distilled off after drying and the residue is fractionated *in vacuo*. The hot cut boiling at 110—112°C/1.5 mmHg is 1 - (3 - bromophenyl) - 2 - methyl - acetylene.

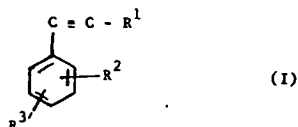
$$n_D^{25}=1.5885.$$

Analysis:

Calculated: Bromine 40.98%
Found: Bromine 41.40%

WHAT WE CLAIM IS:

1. Compounds of the general formula I



wherein

(a) R¹ is alkyl of 5 or 6 carbon atoms or diaralkyl wherein the alkyl moiety has 2—6 carbon atoms;

R² is hydrogen or halogen; and

R³ is hydrogen, alkyl having 1 to 6 carbon atoms, aralkyl having 1 to 6 carbon atoms in the alkyl moiety, aryl or aryloxy or an aroyl group of the general formula ArCO, wherein Ar is phenyl or a 2-thienyl group; with the proviso that R² and R³ are not both hydrogen; or (b) R¹ is hydrogen, alkyl having 1 to 6 carbon atoms, aralkyl wherein the alkyl moiety has 1 to 6 carbon atoms, or diaralkyl wherein the alkyl moiety has 2 to 6 carbon atoms,

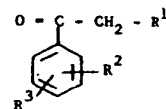
R² is halogen; and

R³ is hydrogen;

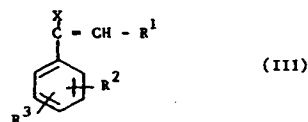
with the provisos that when R¹ is methyl and R³ is hydrogen, R² is not *m*-chloro, *p*-chloro, *p*-bromo or *p*-fluoro.

2. 1 - (3 - Bromophenyl) - 2 - methyl - acetylene.

3. A process for the preparation of the compounds of the general formula I as defined in claim 1, which comprises reacting a compound of the general formula II.



wherein the substituents are as defined in claim 1, with a halogenating agent and reacting the corresponding compounds of the general formula III thus obtained



with a strong base.

4. A process according to claim 3 wherein said halogenating agent is a phosphorus halide.

5. A process according to claim 4 wherein said halogenating agent is phosphorus pentachloride.

6. A process according to claim 5 wherein said compound of general formula (III) is reacted with phosphorus pentachloride at 50° to 90°C in the absence of a solvent.

7. A process according to claim 5 wherein said compound of general formula (III) is reacted with phosphorus pentachloride at 20° to 100°C in the presence of an organic solvent.

8. A process according to claim 7 wherein the reaction temperature is 50° to 90°C.

9. A process according to any of claims 3 to 8 wherein said strong base is an alkali metal hydroxide or alkali metal alcoholate.

10. A process according to claim 9, which

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comprises reacting said compound of the general formula (III) with sodium methoxide in the presence of dimethylsulfoxide or dimethylformamide.

5 11. A process according to any of claims 3 to 10 wherein said compound of the general formula (III) is reacted with a strong base without isolation.

10 12. A process according to claim 3 substantially as illustrated in the Example herein.

13. Compounds according to claim 1 whenever made by the process of any of claims 3 to 12.

14. Compounds according to claim 1 15 wherein R' is other than hydrogen.

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